

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 7

**REMARKS**

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, is respectfully requested, as the changes place the application in condition for allowance.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 8

I. Status of the Claims and Formal Matters

Claims 1-4, 6-11, 13-21 and 53-65 are pending in this application. Claims 1, 3-4, 6-11 13, and 15-21 have been amended, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Original claims 5, 12, and 22-32, as well as claims 45 and 52 have now been cancelled. Claims 43-52 are withdrawn by the Examiner. It is alleged that claims 43-52 relate to subject matter that is outside of the scope of the elected invention; reconsideration of the withdrawal and rejoinder of claims 43, 44 and 46-51, as amended herein, is respectfully requested. New claims 53-65 have been added. No new matter has been added by these amendments. Support for these amendments is found throughout the specification and in the original claims.

It is submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§ 101, 102, 103 and 112. The amendments to the claims herein are not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather the addition and amendments to the claims are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

Withdrawal of the previous rejection under 35 U.S.C. § 112 (second paragraph) is acknowledged. The Examiner is thanked for his attention to this matter, and for his helpful comments during the telephonic interview on September 14, 2004.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 9

## II. Withdrawal of Claims 43-53

Claims 43-53 were withdrawn on the grounds that they are independent or distinct from the invention originally claimed. Applicants respectfully traverse the withdrawal of claims 43, 44 and 46-51.

Constructive election of the original claims as filed did not exclude the subject matter of claims 43, 44 and 46-51 because claims 43, 44 and 46-51 reverse the order in which the steps of the invention are carried out without changing the end result of the claimed methods (i.e., promoting cell death). The M.P.E.P. directs the search and examination of an entire application “[i]f the search and examination of an entire application can be made without serious burden, ... even though it includes claims to distinct or independent inventions.” *Id.* It is respectfully submitted that it would not place an unnecessary burden on the Examiner to search and examine claims 43, 44 and 46-51 together with claims 3 and 15, as a search for the methods of claims 43, 44 and 46-51 would inevitably encompass claims 3 and 15.

Reconsideration of the withdrawal and rejoinder of claims 43, 44 and 46-51, as amended herein, is respectfully requested.

## III. The Rejections Under 35 U.S.C. § 112 Are Overcome

Claims 1-2, 4, 6-14, 16-21 and 33-42 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. This rejection is respectfully traversed.

The amendments to claims 1, 2, 13 and 14 (and thus dependent claims 4, 6-14, 16-21) and new claims 33-42 were deemed to contain new matter. Applicants maintain that the amendments and new claims are fully supported by the instant specification. In the interest of furthering prosecution, the rejected claim terms have been deleted, and claims 12 and 33-42 have been canceled. Accordingly, the amendments presented herein are fully responsive to this rejection. Withdrawal of the rejection of claims 1-2, 4, 6-11, 13-14 and 16-21 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement is respectfully requested.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 10

Claims 1-4, 6-21 and 33-42 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. This rejection is respectfully traversed.

The nature of the rejection relates to the scope of the claims. In particular, the terms "cytotoxic agent," "inhibitors of vacuolar proton ATPase activity," "inhibitors of acidic vesicular function or acidification," and "macrolide" are alleged to create the need for undue experimentation in practicing the methods of the claimed invention. Applicants maintain that claims 1-4, 6-21 and 33-42 are fully supported by the instant specification. In the interest of furthering prosecution, the rejected claim terms have been deleted, and claims 12 and 33-42 have been canceled.

In particular, the Examiner's attention is directed to the amendments of claims 1, 3, 13 and 15. In claims 1 and 13, "cytotoxic agent" is replaced by "chemotherapeutic agent." In claims 1, 3, 13 and 15, the terms "inhibitors of vacuolar proton ATPase activity" and "inhibitors of acidic vesicular function or acidification" have been replaced by "a plecomacrolide or a benzolaetone enamide" that has the desired inhibitory function. Amended claims 1, 3, 13 and 15, and the claims depending therefrom, do not require undue experimentation.

The present invention is directed to methods for increasing the sensitivity of neoplastic cells to traditional courses of radiation or chemotherapy through administration of compounds that inhibit vacuolar proton ATPase activity or acidic vesicular function/acidification. Chemotherapeutic agents are well known in the art, and standard methods of administration are employed by methods of the invention. Exemplification for at least four chemotherapeutic agents is provided in the instant specification (adriamycin, rapamycin, etoposide and tamoxifen).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976). If needed, one of skill in the art could conduct routine experimentation according to methods known in the art or as taught by the instant specification to evaluate the potential of any candidate chemotherapeutic agent. Thus, it is well within the level of ordinary skill in the art to select and administer chemotherapeutic agents according to the methods of the invention.

The invention is based, in part, on the observation that the accumulation of acidic vesicular organelles resulting from irradiation and chemotherapy can be prevented, thereby further enhancing cell death. This can be achieved by providing agents that are inhibitors of

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 11

vacuolar proton ATPase activity or acidic vesicular function/acidification in conjunction with irradiation and chemotherapy. Amended claims 1, 3, 13 and 15 (as well as new claim 66) now specify that the agents are plecomacrolides or benzolaetone enamides that have the desired inhibitory function. Support for this recitation can be found on page 4, paragraph 0007 and page 8, paragraph 0017 of the specification, as well as in item numbers 1, 24, 15 of the Information Disclosure Statement filed on February 6, 2003. Exemplification for the plecomacrolides bafilomycin and concanamycin and the benzolaetone enamide salicylihalamide A are provided in the instant specification. Moreover, plecomacrolides and benzolaetone enamides are known in the art to be specific inhibitors of vacuolar proton ATPases. Thus, selection of a suitable plecomacrolide or benzolaetone enamide that is an inhibitor of vacuolar proton ATPase activity or acidic vesicular function/acidification would not involve undue experimentation.

Withdrawal of the rejection of claims 1-4, 6-21 and 33-42 under 35 U.S.C. § 112, first paragraph for lack of enablement is respectfully requested.

Claims 1-4, 11-16, 33-35, 37 and 41-42 are rejected under 35 U.S.C. § 112, 2<sup>nd</sup> paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. This rejection is respectfully traversed.

Claims 1-4, 11-16, 33-35, 37 and 41-42 are alleged to be indefinite for failing to structurally, formulaically or nomenclaturally identify the "active agent." It is disputed that "inhibitors of vacuolar proton ATPase activity" or "inhibitors of acidic vesicular function or acidification" must be defined according to a chemical structure or formula. However, in the interest of furthering prosecution, claims 1, 3, 13 and 15 have now been amended to specify that the "active agent" is a plecomacrolide or a benzolaetone enamide. Withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

In view of the amendments and arguments presented herein, withdrawal of all rejections under 35 U.S.C. § 112 is respectfully requested. As discussed during the telephonic interview on September 14, 2004, it is believed that withdrawal of the rejections under § 112 against claims 3 and 15 and the claims depending therefrom will result in allowance of these claims. If any issue under § 112 remains as an impediment to allowance of claims 3 and 15, the Examiner is requested to contact the undersigned.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 12

#### IV. The Rejections Under 35 U.S.C. § 102(b) Are Overcome

Claims 1, 2, 4-8, 11-14 and 16-19 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Altan *et al.* (Document 18 of IDS submitted February 10, 2003, hereinafter "Altan"). This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein. The cited reference does not anticipate the instant invention.

A prior art reference under 35 U.S.C. §102(b) must contain all elements of the claimed invention. See *Lewmar Marine Inc. v. Barent Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Altan does not disclose all elements of the claimed methods, and therefore fails as a reference under under 35 U.S.C. §102(b).

Altan relates to defective acidification in adriamycin-resistant cells. Altan disrupts the acidification of organelles in resistant cells with monensin, bafilomycin A1 or concanamycin A to change the adriamycin distribution to that found in drug-sensitive cells, rendering the cell vulnerable once again to chemotherapy (see, e.g., Summary of Altan). In other words, Altan illustrates the disruption of acidic organelles that have already formed within the cell to sequester and store adriamycin, thereby rendering the cell adriamycin-resistant. Altan illustrates the conversion of drug resistant cells to non drug resistant cells by redistribution of adriamycin (see, e.g., page 1594, left column, first two paragraphs of Altan).

Amended claims 1 and 13 recite contacting a cell with a plecomacrolide or a benzolaetone enamide within about 48 hours of the first exposure to a chemotherapeutic agent to prevent formation of acidic vesicular organelles (support for this recitation can be found on page 12, paragraph 0029, page 51 and page 60 of the specification). The MCF-7/ADR cells of Altan were subjected to continuous dosing of adriamycin until the drug resistant phenotype developed and after selection, were cultured in the presence of 0.8 µm adriamycin. Altan fails to disclose any methods involving treatment with a plecomacrolide or a benzolaetone enamide within about 48 hours of the first exposure to a chemotherapeutic agent. Thus, Altan does not contain each and every element of the claimed methods. It is submitted that the rejection of claims 1 and 13 have been obviated. Since claims 2, 4-8, 11, 12, 14 and 16-19 depend from claims 1 or 13, it is submitted that the rejections to claims 2, 4-8, 11, 12, 14 and 16-19 have also been obviated.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 13

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) are earnestly requested.

V. The Rejections Under 35 U.S.C. § 103(a) Are Overcome

Claims 9, 10, 20 and 21 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Altan in view of Boyd et al. (reference 1 of the IDS submitted February 10, 2003, hereinafter "Boyd"). This rejection is respectfully traversed. This rejection is moot in light of the amendments to the claims submitted herein. The claimed methods are not obvious in view of the cited references.

The Examiner alleges that Altan teaches a method of administering monensin, baflomycin A1 or concanamycin to a cell which is resistant to adriamycin from previous therapies to sufficiently change the cell to that of a drug-sensitive cell, thereby rendering the cell vulnerable once again to chemotherapy. Administration of a benzolactone enamide or salicylyhalamide A is not taught by Altan. Boyd discloses that benzolactone enamides, including salicylyhalamide A, are inhibitors of vacuolar proton ATPase activity in tumor cells. It is alleged to have been obvious for one of ordinary skill in the art to administer a compound (salicylyhalamide A) which has an art recognized activity (inhibition of vacuolar proton ATPase activity) for another compound (baflomycin) which has the same art recognized activity in a correlative method.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981 (C.C.P.A. 1974). The combination of Boyd with Altan fails to teach or suggest any methods involving treatment with a plecomacrolide or a benzolactone enamide within about 48 hours of the first exposure to a chemotherapeutic agent.

Boyd relates to the discovery of a novel class of benzolactone enamides and merely discloses that such benzolactone enamides selectively inhibit vacuolar proton ATPase activity. Boyd does not correct the deficiency of Altan because there is no teaching, suggestion or motivation in Boyd to contact a cell with an inhibitor prior to an accumulation of acidic vesicular organelles in the cell. Accordingly, the combination of Altan and Boyd does not teach or suggest all elements of the claimed methods.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 14

It is submitted that the rejection of claims 9, 10, 20 and 21 has been obviated.  
Reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) are earnestly  
requested.

Paglin et al.  
U.S. Serial No. 10/006,957  
Page 15

**REQUEST FOR INTERVIEW**

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

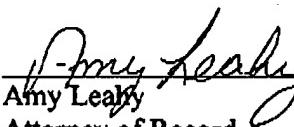
Paglin et al.  
U.S. Serial No. 10/006,957  
Page 16

**CONCLUSION**

In view of the amendments and remarks herewith, the application is in condition for allowance. Favorable reconsideration of the application, reconsideration, and withdrawal of the objections to and rejections of the application, and prompt issuance of a Notice of Allowance are respectfully requested.

Respectfully submitted,

October 15, 2004

  
Amy Leaky  
Attorney of Record  
Reg. No. 47, 739  
EDWARDS & ANGELL, LLP  
Intellectual Property Practice Group  
P.O. Box 9169  
Boston, MA 02209  
Telephone: (203) 353-6839

PTO/SB/97 (12-97)

Approved for use through 9/30/00. OMB 0651-0031

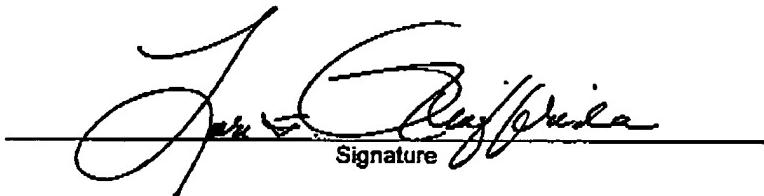
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## Certificate of Transmission Under 37 CFR 1.8

I hereby certify that this correspondence is being facsimile transmitted to the United States Patent and Trademark Office

on October 15, 2004  
Date



\_\_\_\_\_  
Signature

Lori J. Giuffrida  
Typed or printed name of person signing Certificate

Note: Each paper must have its own certificate of transmission, or this certificate must identify each submitted paper.